Highly Stereoselective Oxidative Esterification of Aldehydes with β-Dicarbonyl Compounds

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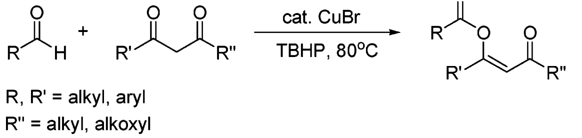
Received March 20, 2006

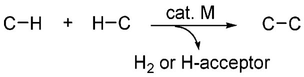


Copper-catalyzed oxidative esterification of aldehydes with β-dicarbonyl compounds was developed using *tert*-butyl hydroperoxide as an oxidant. In general, the enol esters were synthesized in good yields (up to 87%) and high stereoselectivity under the optimized reaction conditions.

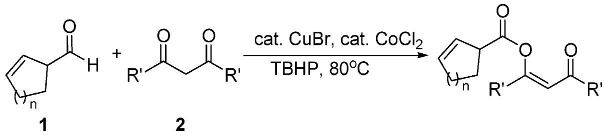
The development of efficient methods for bond formation processes is of great interest to chemists. Carbon−carbon (C−C) bond formation often involves prefunctionalized starting materials and thus requires additional synthetic steps toward the formation of a single chemical bond. The direct utilization of carbon−hydrogen (C−H) bonds to from C−C bonds would be highly desirable since it would eliminate prefunctionalization of the substrates and make synthetic steps shorter. With respect to this goal, we and others have been developing cross-dehydrogenative coupling (CDC) reactions for C−C bond formation (Scheme 1).[1]

During the course of our investigations on the CDC reaction between cyclic alkene substrates **1** with activated methylene compounds **2**,[1c] we uncovered an interesting competing reaction pathway when an aldehyde was introduced into the system. With catalytic amounts of copper and cobalt salts, in the presence of an oxidant such as *tert*-butyl hydroperoxide (TBHP), oxidative esterification of the aldehyde occurred (Scheme 2).

SCHEME 1. CDC Reactions for C−C Bond Formation



SCHEME 2. Oxidative Esterification of Aldehydes



Traditionally, synthesis of esters often involves the nucleophilic addition of an alcohol to activated carboxylic acid derivatives such as acid anhydrides or chlorides.[2] Direct oxidative transformation of an aldehyde moiety to an ester has been accomplished in a variety of ways, such as electrochemical oxidation or through the use of transition metals as catalyst in the presence of an oxidant.[3] Often, these procedures involve the use of a large excess of reagents and expensive catalysts. Furthermore, competing side reactions, such as the oxidation of the alcohol and aldehyde substrates, complicate matters.

Recently, there has been a concerted effort in developing facile conversion of aldehydes to esters. Such protocols involve the use of Oxone,[4] pyridinium hydrobromide perbromide,[5] I_2,[6] Al_2O_3/CH_3SO_3H,[7] and H_2O_2[8] as oxidants for the esterification of aldehydes. While these methods have been demonstrated to be useful for simple alcohol substrates, to the best of our knowledge, there are no published examples in which a β-dicarbonyl or its corresponding enol form are used as substrates for oxidative esterification. As part of our continuing interest in the utilization of C−H bonds for bond formation processes, we wish to report an effective copper-catalyzed oxidative esterification of aldehydes with β-dicarbonyl compounds.

To begin our study, the effect of the various reaction parameters on the oxidative esterification of benzaldehyde **3a** with β-diketone **4a** was examined (Table 1). Initially, on the basis of our earlier report[1a] on the CDC reaction of allylic C−H bond with activated methylene compounds, the combination of CuBr and $CoCl_2$ was examined as cocatalyst (entry 1). Subsequently, it became apparent that $CoCl_2$ was not required for the esterification reaction (entry 2). Furthermore, decreasing

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(1) For representative examples, see the following. sp^3 C−H and sp^3 C−H: (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 56. (b) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (c) Zhang, Y.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1949. (d) Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242. sp^3 C−H and sp C−H: (e) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997. (f) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (g) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312. (h) Murata, S.; Teramoto, K.; Miura, M.; Nomura, M. *J. Chem. Res. Miniprint* **1993**, 2827. sp^2 C−H and sp^2 C−H: (i) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (j) Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2004**, *6*, 4623. (k) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476. (l) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (m) Tsuji, J.; Nagashima, H. *Tetrahedron* **1984**, *40*, 2699. (n) DeBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556. sp C−H and sp C−H: (o) Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. *J. Am. Chem. Soc.* **1982**, *104*, 5558.

(2) Larock, R. C. *Comprehensive Organic Transformation*; VCH: New York, 1999.

(3) For representative examples, see: (a) Chiba, T.; Okimoto, M.; Naga, H.; Taka, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 335. (b) Wuts, P. G. M.; Bergh, C. L. *Tetrahedron Lett.* **1986**, *27*, 3995. (c) Connor, B.; Just, G. *Tetrahedron Lett.* **1987**, *28*, 3235. (d) Murahashi, S.; Naota, T.; Ito, K.; Maeda, Y.; Taki, H. *J. Org. Chem.* **1987**, *52*, 4319. (e) William, D. R.; Klingler, F. D.; Allen, E. E.; Lichtenthaler *Tetrahedron Lett.* **1988**, *29*, 5087. (f) Marko, I. E.; Mekhalfia, A.; Ollis, W. D. *Synlett* **1990**, 347. (g) Okimoto, M.; Chiba, T. *J. Org. Chem.* **1998**, *53*, 218. (h) Espenson, J. H.; Zuolin, Z.; Zauche, T. H. *J. Org. Chem.* **1999**, *64*, 1191. (i) Kiyooka, S.; Ueno, M.; Ishii, E. *Tetrahedron Lett.* **2005**, *46*, 4639.

(4) Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031.

(5) Sayama, S.; Onami, T. *Synlett* **2004**, 2739.

(6) (a) Mori, N.; Togo, H. *Tetrahedron* **2005**, *61*, 5915. (b) Inch, T. D.; Ley, R. V.; Rich, P. *J. Chem. Soc. C* **1968**, 1693. (c) Eliel, E. L.; Clawson, L.; Knox, D. E. *J. Org. Chem.* **1985**, *50*, 2707.

(7) Sharghi, H.; Sarvari, M. H. *J. Org. Chem.* **2003**, *68*, 4096.

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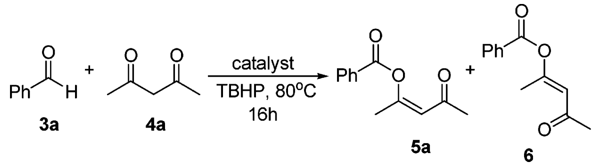
10.1021/jo0606103 CCC: $33.50

TABLE 1. Optimization of Reaction Conditions[a]



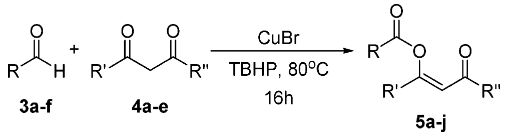
entry	catalyst	yield (%) of **5a**[b]	yield (%) of **6**[b]	conversion[c] (%)
1[d]	CuBr/CoCl$_2$	51	10	100
2[d]	CuBr	51	10	100
3	CuBr	64	7	92
4[e]	CuBr	53	10	83
5	CuCl	54	18	100
6	CuI	26	9	70
7	CuBr$_2$	54	7	95
8	Cu(OAc)$_2$	49	19	91
9	Cu(OTf)$_2$	0	0	95
10	CuOTf[f]	0	0	95

[a] Benzaldehyde (1 equiv), 2,4-pentanedione (1.1 equiv), TBHP (1.5 equiv), cobalt(II) chloride (10.0 mol %), and copper salt (2.5 mol %). [b] Reported yields were based on benzaldehyde and determined by NMR using as internal standard. [c] Conversion was based on benzaldehyde. [d] TBHP (2.0 equiv). [e] TBHP (1.0 equiv). [f] As a toluene complex.

the amount of TBHP to 1.5 equiv improved the yield (entry 3). After a variety of copper salts were screened, CuBr was found to be the most effective (entries 3 and 5−9).[9] Attempts to improve the yield through the use of different oxidants (O$_2$, H$_2$O$_2$, cumene hydroperoxide, *tert*-butyl peroxybenzoate, etc.) and solvents (toluene, dioxane, DMSO, water, etc.) were unsuccessful. The reaction temperature played an important role in the esterification. At lower temperatures (20, 50 °C) lower yields were obtained, while increasing the temperature to 100 °C resulted in the complete loss of stereoselectivity with no improvement in the overall yield.

Under the standard conditions, various β-dicarbonyl compounds **4a**−**f** were used as substrates for the oxidative esterification of aldehydes **3a**−**f** (Table 2). In general, the reaction proved to be highly stereoselective for the (*Z*)-enol esters **5a**−**j**, and the level of stereoselectivity was dependent on the nature of the β-dicarbonyl substrates. With β-diketones, the level of stereoselectivity varies (entries 1−2). However, with β-ketoesters **4c**−**e**, the oxidative esterification was shown to be highly stereoselective to furnish (*Z*)-enol esters exclusively (entries 3−11). When the reaction was carried out with substituents on the active methylene position, the desired ester was not obtained. Both aliphatic and aromatic aldehydes were amenable to the reaction conditions and the electronic nature of the aldehydes did not appear to greatly influence the yield of the reaction. When the reaction was extended to simple primary alcohol systems such as 1-butanol, the oxidative esterification also proceeded, albeit at a lower yield (Scheme 3). Furthermore, when a cyclic β-diketone was subjected to the optimized reaction conditions, esterification was not observed. Thus, it appears that substrates that can bind to the copper metal in a bidentate fashion, such as β-diketones and β-ketoesters, are good substrates for the esterification reaction.

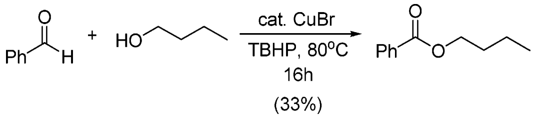
TABLE 2. Copper-Catalyzed Oxidative Esterification of Aldehydes[a]



entry	aldehyde	R	β-dicarbonyl	R′	R″	prod	yield[b] (%)
1	**3a**	Ph	**4a**	Me	Me	**5a**	57[c]
2	**3a**	Ph	**4b**	Et	Et	**5b**	80
3	**3a**	Ph	**4c**	Me	OMe	**5c**	84
4	**3a**	Ph	**4d**	CH$_2$Cl	OEt	**5d**	49
5	**3a**	Ph	**4e**	Ph	OEt	**5e**	86
6	**3b**	4-F−C$_6$H$_4$	**4c**	Me	OMe	**5f**	81
7	**3c**	4-OMe-C$_6$H$_4$	**4c**	Me	OMe	**5g**	81
8	**3d**	C$_5$H$_{11}$	**4c**	Me	OMe	**5h**	72
9	**3e**	cyclohexyl	**4c**	Me	OMe	**5i**	80
10	**3f**	CH(CH$_2$CH$_3$)$_2$	**4c**	Me	OMe	**5j**	89

[a] Aldehyde (1 equiv), β-carbonyl (1.1 equiv), CuBr (2.5 mol %), and TBHP (1.5 equiv). [b] Isolated yields were based on the aldehyde. [c] The (*E*)-stereoisomer was also isolated with a yield of 9%.

SCHEME 3. Oxidative Esterification of a Simple Alcohol



Possible reaction mechanisms to explain the results of the copper-catalyzed oxidative esterification of aldehydes with β-dicarbonyl compounds are proposed in Scheme 4. Copper complex **6** generated from a copper salt with β-dicarbonyl compounds **4a**−**e** may coordinate with aldehydes **3a**−**f** and undergo an internal nucleophilic addition to form copper hemiacetal **7**. H-abstraction of copper complex **7** by a radical generated from the copper-catalyzed decomposition of TBHP followed by a single-electron transfer (SET) of the hemiacetal radical to the copper metal leads to the desired ester **5a**−**j**.[10] Alternatively, copper complex **6** can decompose TBHP to generate a radical, which can then abstract the hydrogen of aldehydes **3a**−**f**. The newly formed acyl radical can undergo SET with copper to produce a Cu(III) complex **8** that can reductively eliminate to release the desired ester **5a**−**j**.[11] For metal-catalyzed oxidation reactions involving TBHP, a radical mechanism is often invoked. Indeed, the introduction of a radical scavenger, 2,6-di-*tert*-butyl-4-methyl phenol (BHT), to the reaction between aldehyde **3a** and β-diketone **4a** prevented the esterification process and provided only trace amounts of **5a** with nearly quantitative recovery of the unreacted aldehyde **3a**.

In conclusion, we have developed a copper-catalyzed oxidative esterification between an aldehyde and a β-dicarbonyl compound using TBHP as an oxidant. The reaction was found to be highly stereoselective to provide the enol esters in good yields. Further investigations into the scope, mechanism, and

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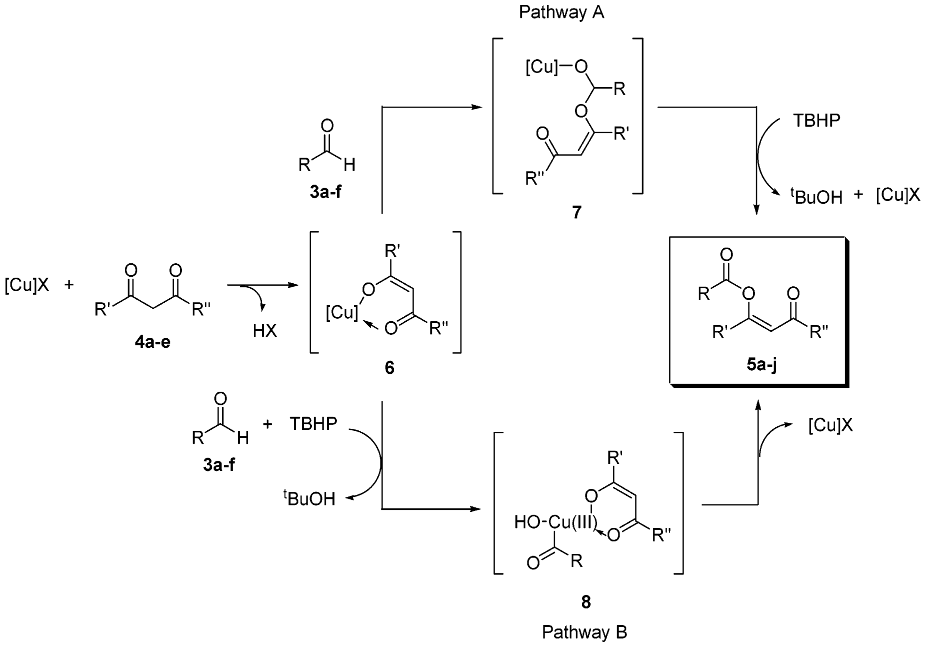
(9) Both Cu(I) and Cu(II) salts were viable catalysts for the esterification reaction. However, the oxidation state of the active catalytic species cannot be predicted due to the ability of Cu(I) salts to oxidatively, and Cu(II) salts to reductively, decompose peresters to generate radicals. See: Sheldon, R. A.; Kochi, J. K. *Metal-catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981.

(10) SET of ketyl radical intermediates have been proposed in the oxidation of alcohols to aldehydes by galactose oxidases. For recent mechanistic studies, see: (a) Himo, F.; Eriksson, L. A.; Maseas, F.; Siegbahn, P. E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8031. (b) Whittaker, M. M.; Ballou, D. P.; Whittaker, J. W. *Biochemistry* **1998**, *37*, 8426. (c) Wachter, R. M.; Montague-Smith, M. P.; Branchaud, B. P. *J. Am. Chem. Soc.* **1997**, *119*, 7743.

(11) Copper(III) intermediates have been proposed for copper-catalyzed allylic oxidation of alkenes with peresters. See: Eames, J.; Watkinson, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3567.

SCHEME 4. **Proposed Mechanism for Copper-Catalyzed Oxidative Esterification of Aldehydes**



synthetic application of this reaction are currently under investigation in our laboratory.

Experimental Section

General Procedure for the Copper-Catalyzed Oxidative Esterification of Aldehydes with β-Dicarbonyl Compounds. To a mixture of CuBr (3.3 mg, 0.025 mmol, 2.5 mol %), aldehyde **3a** (0.100 mL, 0.985 mmol), and β-diketone **4a** (0.11 mL, 1.1 mmol) was added *tert*-butyl hydroperoxide (TBHP, 5.5 M in decanes, 0.27 mL, 1.5 mmol) under an inert atmosphere (N_2) at room temperature. The reaction vessel was capped and stirred overnight at 80 °C. The crude reaction mixture was purified by column chromatography on silica gel (EtOAc/hexane = 1:4) to provide **6** (18.3 mg, 0.0896 mmol, 9%) and **5a** (114.0 mg, 0.558 mmol, 57%) as a clear colorless oil.

(*Z*)-4-Oxopent-2-en-2-yl benzoate (6): R_f 0.44 (EtOAc/hexane = 1:4); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (m, 2H), 7.63 (m, 1H), 7.49 (m, 2H), 6.23 (s, 1H), 2.45 (s, 3H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.1, 163.7, 162.7, 133.7, 129.9, 128.9, 128.5, 116.5, 32.3, 18.8. The spectral data are consistent with those reported in the literature.[12]

(*Z*)-4-Oxopent-2-en-2-yl benzoate (5a) (Table 2, entry 1): R_f 0.30 (EtOAc/hexane = 1:4); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (m, 2H), 7.69 (m, 1H), 7.58 (m, 2H), 5.99 (s, 1H), 2.29 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.0, 163.1, 157.8, 133.5, 129.9, 128.7, 128.4, 117.1, 31.0, 21.5. The spectral data are consistent with those reported in the literature.[12]

Acknowledgment. We thank the Canada Research Chair (Tier I) foundation (to C.J.L.), the CFI, NSERC, and CIC (AstraZeneca/Boehringer Ingelheim/Merck Frosst) for support of our research.

Supporting Information Available: Representative experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0606103

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[12] Negishi, E.; Liou, S.; Xu, C.; Shimoyama, I.; Makabe, H. *J. Mol. Catal. Chem. A.* **1999**, *143*, 279.